Respiratory Syncytial Virus (RSV) vaccines

Kim Mulholland
MCRI
RSV

- Discovered in 1956 ("Chimpanzee Coryzal Agent")
- Identified from children with lower respiratory tract infections, especially wheeze
- Dominant paediatric respiratory pathogen in the world
- But no vaccine ... why?
What we know about RSV disease

▶ In infants
  – Acute bronchiolitis (most cases due to RSV)
  – Pneumonia
  – Laryngotracheobronchitis (croup)
  – Causes seasonal epidemics, every winter

▶ Older children and adults
  – Minor ARIs, sometimes with wheeze

▶ Elderly
  – More severe respiratory illness, maybe significant mortality
RSV bronchiolitis

RSV hospitalizations in California 2000-2006

about half with CHD

### Severity of bronchiolitis

<table>
<thead>
<tr>
<th>Assessment of the severity of bronchiolitis in infants &lt;12 months Adapted from [41,55]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Feeding</strong></td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Respiratory rate</td>
</tr>
<tr>
<td>Chest wall indrawing</td>
</tr>
<tr>
<td>Nasal flare or grunting</td>
</tr>
<tr>
<td>Sp02</td>
</tr>
<tr>
<td>General behavior</td>
</tr>
</tbody>
</table>
# Severe RSV LRTI

An infant or young child presenting to a health facility that is part of the case ascertainment system for the phase III trial who fulfills both the laboratory AND clinical criteria below:

### Laboratory criterion
- RSV infection as confirmed by a fit-for-purpose, fully validated PCR assay with high specificity and sufficient sensitivity on upper respiratory samples

### Clinical criteria
- Respiratory infection defined as cough or difficulty breathing
- LRTI defined as fast breathing by WHO criteria or \( \text{SpO}_2 < 95\% \)
- \( \geq 1 \) of the following features of severe disease
  - Pulse oximetry < 93%
  - Lower chest wall in-drawing

---

# Very severe RSV LRTI

An infant or young child presenting to a health facility that is part of the case ascertainment system for the phase III trial who fulfills both the laboratory AND clinical criteria below:

### Laboratory criterion
- RSV infection as confirmed by a fit-for-purpose, fully validated PCR assay with high specificity and sufficient sensitivity on upper respiratory samples

### Clinical criteria
- Respiratory infection defined as cough or difficulty breathing
- LRTI defined as fast breathing by WHO criteria OR \( \text{SpO}_2 < 95\% \)
- \( \geq 1 \) of the following features of very severe disease
  - Pulse oximetry < 90%
  - Inability to feed
  - Failure to respond/unconscious
High risk groups

› Ex-premature infants
  – High risk of severe disease
  – Reasons unclear – poor immunity, narrow airways

› Congenital heart disease
  – Especially those with significant haemodynamic problems

› At RCH over 100 ICU admissions/year
  – ~57% are full term healthy infants
  – Preterm infants have longer respiratory support
**RCH DATA**

- **p=0.0024 (mann-whitney)**

![Graph 1](Image 1)

- **p=0.004**

![Graph 2](Image 2)
CHD – longer admissions with RSV - California

Immunity to RSV

› Protective
  – High maternal antibody levels
  – Breast feeding

› Natural infection provides some immunity, but…
  – Repeated infections in the same season are quite common

› Vaccination needs to be superior to natural immunity
Formalin Inactivated RSV vaccine

History of FI-RSV Vaccine Enhanced Disease in Clinical Trials

<1966 – Live and inactivated RSV given parenterally without benefit

1966-7 – 4 independent studies using Pfizer lot 100 formalin-inactivated RSV did not protect and caused enhanced disease

>1967 - Live RSV IM, live-attenuated RSV IN given without harm

Subunit F (F+G+M, FG, F+G) and G (BBG2Na) given to adults and children with pre-existing immunity (2-3 fold rise in NT; >10-20 fold rise in ELISA titers)
**FI-RSV vaccine – enhanced disease**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>n</th>
<th>Infected (%)</th>
<th>Hospitalized (%)</th>
<th>Deaths**</th>
</tr>
</thead>
<tbody>
<tr>
<td>FI- RSV</td>
<td>31</td>
<td>20 (65)</td>
<td>16 (80)</td>
<td>2</td>
</tr>
<tr>
<td>FI-PIV-1</td>
<td>40</td>
<td>21 (53)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Vaccine produced binding antibody, non-functional
- Th2 biased immune response

*Kim et al. Am J Epidemiol 1969;89:422*
1990s – Two vaccines developed (Wyeth)

› F-protein vaccine
  - Trials in adults, older children
  - Cystic fibrosis patients – less severe disease
  - Pregnant women (Texas) – 35 women recruited
    (Vaccine. 2003 Jul 28;21(24):3465-7)
  - No trials in sero-negative infants

› Live attenuated vaccine
  - Tested in infants
  - Caused URI symptoms
  - Immune responses poor
Palivizumab – monoclonal RSV antibody

› Palivizumab (licensed 2003)
  - an anti-RSV, humanized murine, monoclonal antibody
  - Administered as monthly injections during the season
  - Reduces RSV-admission risk by 45-55% in high risk groups
  - Very expensive – used sparingly in Melbourne

› New generation products
  - Long-lasting – single dose/season
    › Company wants this approved for all US infants
  - Generic products on the way
Vaccine progress – Regulatory position

› Sub-unit vaccines
  – Suitable for adult immunization
  – Suitable for maternal immunization

› Live attenuated vaccines
  – Suitable for infants
RSV proteins
F-protein – Pre and Post Fusion structure

Value as target for potent neutralizing antibody
- Outstanding
- Excellent
- Good
- Poor

Site Ø
Site II
Site IV
Six-helix bundle

Prefusion F
Postfusion F

B Graham, WHO Consultation on RSV Vaccine Development March 23-24, 2015
Current vaccine approaches

› Live attenuated – 5
› Live vectored – 1
› F sub-unit - 7
### F Protein vaccines

#### Postfusion F

<table>
<thead>
<tr>
<th>Developer</th>
<th>Phase</th>
<th>Populations (tested)</th>
<th>Populations (target)</th>
<th>Adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novavax</td>
<td>2</td>
<td>18-49 y.o., elderly, pregnant women, children 24-71 mos.</td>
<td>elderly, pregnant women, children 24-71 mos.</td>
<td>Alum</td>
</tr>
<tr>
<td>Medimmune</td>
<td>1</td>
<td>elderly</td>
<td>elderly</td>
<td>GLA-Se</td>
</tr>
<tr>
<td>Novartis</td>
<td>1</td>
<td>18-45 y.o.</td>
<td>pregnant women, elderly?</td>
<td>Alum/MF59</td>
</tr>
</tbody>
</table>

#### Prefusion F

<table>
<thead>
<tr>
<th>Developer</th>
<th>Phase</th>
<th>Population (tested)</th>
<th>Population (target)</th>
<th>Adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK</td>
<td>1</td>
<td>men; women</td>
<td>pregnant women</td>
<td>Alum +/-</td>
</tr>
<tr>
<td>NIH/VRC</td>
<td>Preclinical → 1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Novavax – F nano-particle vaccine

- Only vaccine in Phase 3 trials –
  - Adult immunization – protect the elderly
  - Maternal immunization – protection against infant infection

- Adult phase 3 trial results –
  - No efficacy in elderly
  - 28/5892 in vaccine recipients; 26/5917 in placebo recipients

- Maternal immunization study –
  - Trial underway in USA, New Zealand, South Africa, Chile and other sites
    - Plans to use Philippines site (only Asian site)
    - Sample size 8618 over 4 years
  - Endpoint – infant severe LRTI
Live attenuated RSV vaccines

› NIH – RSV LID ΔM2-2

› Modification of the live attenuated RSV vaccine of the 90s:
  - Reduced replication capacity
  - Enhanced expression of F-protein

› Small studies in 29 seronegative US infants
  - No increase in ARI symptoms
  - Modest immune responses
GSK approach

› Maternal vaccine – F protein
› Infant vaccines – Ad vector approach
RSV paediatric vaccine candidate: novel vector approach

ChAd & MVA encoding RSV F, N & M2-1 proteins

Open label dose escalation study in healthy adults (NCT01805921)

Experimental groups
1. PanAd3-RSV IM / MVA-RSV IM
2. PanAd3-RSV IM / PanAd3-RSV IM
3. PanAd3-RSV IN / MVA-RSV IM
4. PanAd3-RSV IN / PanAd3-RSV IM

Doses
PanAd3-RSV: Low $5 \times 10^8$ and High $5 \times 10^{10}$ vp
MVA-RSV: Low $1 \times 10^7$ and High $1 \times 10^8$ pfu

10 volunteers/group
(2 & 8 volunteers at low & high dose)

The vaccine candidates were well tolerated & immunogenic
Fig. 2. RSV vaccine clinical development pathway for pregnant women.
RSV vaccines offer the prospect of a major impact on:
- Infant bronchiolitis
- Long term complications – asthma, COAD?
- Health systems
- Severe disease in the elderly

Over the next 5 years several will enter phase 3 trials – both maternal and infant